Fidaxomicin for the Treatment of *Clostridium difficile*-Associated Diarrhea (CDAD)

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Anti-Infective Drugs Advisory Committee
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NDA 201,699 / Fidaxomicin

- Submitted by Optimer Pharmaceuticals, Inc on November 29, 2010
- Treatment of *Clostridium difficile*-associated diarrhea (CDAD) in adults
- A macrolide supplied as 200-mg tablets
- Proposed regimen: 200 mg PO BID x 10 days

Clinical Development

- Two randomized (1:1) double-blind trials
  - 101.1.C.003 5/2006 – 8/2008 US/Canada
  - 101.1.C.004 4/2007 – 12/2009 US/Canada/EU
- Comparator: vancomycin 125 mg PO q6h for 10 days
- Primary endpoint: Cure rates at the EOT
- Secondary endpoints: Recurrence and Global cure rates within at least 25 days post-treatment

Enrollment Criteria

- Subjects ≥ 16 years of age with >3 unformed bowel movements tested positive *C. difficile* toxin A or B
- < 24 hours of pretreatment with vancomycin or metronidazole

Excluded:

- Life-threatening CDAD defined as WBC >30 × 10^9 /L, T >40°C, septic shock, peritoneal signs, or significant dehydration
- Toxic megacolon

Safety Population for Fidaxomicin Development Program

	Treatment Groups (N of subjects)		
	Fidaxomicin	Vancomycin	Placebo
Any Dose	**676**	**583**	10
Phase 1	64	-	10
Phase 2, dose ranging	48	-	-
Phase 3	**564**	**583**	-
101.1.C.003	300	323	-
101.1.C.004	264	260	-

Exposure to ≥ 1 Dose of Fidaxomicin in All Trials

Daily Dose	100 - 200 mg	300 mg	450 mg	400 mg	Any dose
N of subjects	56	12	11	608	676

- Mean duration of exposure in phase 3 trials was 10.2 days

Summary of Treatment-Emergent Adverse Events in Phase 3 Studies

	Fidaxomicin N=564 n (%)	Vancomycin N=583 n (%)
All TEAEs	385 (68.3)	382 (65.5)
Deaths	36 (6.4)	38 (6.5)
Serious TEAEs	145 (25.7)	135 (23.2)

Most Common TEAEs Resulted in Death in Phase 3 Trials

	Fidaxomicin (N=564) n (%)	Vancomycin (N=583) n (%)
All Deaths	36 (6.4)	38 (6.5)
Sepsis related	5	6
Respiratory failure	4	2
Pneumonia	3	2

Subjects Whose Deaths Could Possibly Be Related to Study Drug Due to Lack of Efficacy

Age Sex	Days on Study Drug	Study Day of Death	Events Contributed to Death
Fidaxomicin			
79 F	11	55	Pseudomembranous colitis
81 F	6	16	Megacolon
89 M	5	12	Gastrointestinal perforation
72 M	4	23	Pseudomembranous colitis
83 M	11	31	Clostridium difficile sepsis
Vancomycin			
74 F	8	10	Septic shock due to CDI
76 M	4	11	Sepsis due to CDI
85 F	7	8	Sepsis due to CDI
50 M	5	33	Recurrence of CDI / Septic shock

Selected TEAEs in Phase 3 Trials

	Fidaxomicin N=564 n(%)	Vancomycin N=583 n (%)
Gastrointestinal hemorrhage	20 (3.5)	12 (2.1)
Overdose and Duodenal perforation	1	0
Megacolon	3	0
Decreases in WBC counts	23 (4.1)	10 (1.7)
Intra-uterine death/Cleft palate	1	0

Additional Discussion Points

- Dropouts and discontinuations
- P-glycoprotein inhibitors interactions

TEAEs Associated with GI Hemorrhage

MedDRA Preferred terns	Fidaxomicin (N=564) n (%)	Vancomycin (N=583) n (%)
Phase 3 trials	**20 (3.5%)**	**12 (2.1%)**
Hematochezia/Diarrhea Hemorrhagic	12	1
Gastrointestinal Hemorrhage	5	1
Rectal/Hemorrhoidal Hemorrhage	3	4
Occult Blood Positive	0	1
Upper GI Hemorrhage	0	3
Ischemic colitis/Large intestine perforation	0	2
Phase 2 trial (N=48), 200 mg group		
Gastrointestinal Hemorrhage	1 (2.1%)	NA

GI Hemorrhage

	Phase 3		Phase 2
	Fidaxomicin N=20 (3.5%)	Vancomycin N=12 (2.1%)	N=1 (2.1%)
Serious	6	5	1
Fatal	1	0	-
Resulted in Withdrawal	2	0	-

GI Hemorrhage in Phase 3 trials

	Fidaxomicin N=20	Vancomycin N=12
Severe CDAD at baseline	7 /142 (4.9%)	2 /150 (1.3%)
Non-Severe CDAD at baseline	13 /422 (3.1%)	10 /433 (2.3%)
Occurred After Study Drug Stopped	12	8
Likely Upper GI-hemorrhage	2	4
Likely Lower GI-hemorrhage	14	6

Overdose/Duodenal perforation

- A 64-yo male with no history of peptic ulcer disease received all four doses of study drug at once on study day 3; no immediate reactions; withdrawn from the study
- PMH: Renal cell cancer with spinal metastases, CAD, HTN, hyperlipidemia
- Meds: Enteric coated aspirin, atorvastatin, metoprolol, and IV potassium chloride
- Study day 4: hypotension, anuria; required intubation
- Study day 5: perforated duodenal ulcer found at surgery
- Subsequent recovery

Megacolon

- Reported only in the fidaxomicin group
- All 3 cases caused by BI *C. difficile* strain
- All subjects had severe CDAD at baseline
- Two subjects failed 3 and 6 days of study drug therapy prior to being diagnosed with megacolon and one subject died
- The 3rd subject received only two doses of study drug prior to colectomy

Pregnancy

- A 19-yo female found to be pregnant on study day 25; negative pregnancy test on study day 1; completed 11 days of fidaxomicin with resolution of CDAD
- PMH: precursor B cell acute lymphocytic lymphoma
- Meds: vincristine and methotrexate 3 weeks prior to enrollment; ceftazidime and clindamycin 2 weeks prior to enrollment

  On study meds: nystatin, chlorhexidine PO, sucralfate, famotidine, and diphenhydramine
- USG at 9 weeks of pregnancy showed 5 live fetuses
- 18 weeks of pregnancy: delivery of 2 deceased and 3 live fetuses; one fetus had a cleft palate

TEAEs Related to Decreases in WBC Counts

	Fidaxomicin N=564 n (%)	Vancomycin N=583 n (%)
Total Subjects	23 (4.1)	10 (1.7)
Neutropenia	14 (2.5)	6 (1.0)
Lymphopenia	11 (1.9)	5 (0.9)
Baseline WBC < 4.0×10^9/L	10 / 23	5 / 10

Decrease in WBC Indices

- 20 out of 23 fidaxomicin subjects had immunosuppressive conditions, sepsis and/or received chemotherapy or prednisone
- No WBC abnormalities in Phase 1 and 2 trials
- No bone marrow toxicity in non-clinical studies

Dropouts and Discontinuations

	Fidaxomicin N= **564**	Vancomycin N=**583**
Treatment phase	**67 (11.9)**	**66 (11.3)**
Adverse event	22 (3.9)	36 (6.2)
Clinical failure	13 (2.3)	5 (0.9)
Follow-up phase	**28 (5.0)**	**37 (6.3)**
Adverse event	22 (3.9)	17 (2.9)
Completed the Study	**492 (87.2)**	**496 (85.1)**

Fidaxomicin and P-glycoprotein Inhibitors Interactions

- Cyclosporine increased fidaxomicin and OP-1118 exposure (AUC) to 1.9- and 4.1-fold, respectively
- P-glycoprotein inhibitors were identified as follows:
  - omeprazole, esomeprazole
  - azithromycin, cefuroxime
  - clotrimazole, ketoconazole, posaconazole
  - diltiazem, verapamil, atorvastatin, carvedilol
  - cyclosporine, paclitaxel
  - atazanavir, lopinavir
  - quinidine
  - cetirizine

Impact of P-gp inhibitor use on Efficacy and Safety: Phase 3 trials

	Fidaxomicin		Vancomycin	
	P-gp Inhibitor Use		**P-gp Inhibitor Use**	
	No	**Yes**	**No**	**Yes**
Clinical Cure	280/311	192/225	290/332	196/232
mITT population	90.0%	85.3%	87.3%	84.5%
Global Cure	249/311	157/225	221/332	139/232
mITT population	80.1%	69.8%	66.5%	59.9%
Subjects with ≥ 1 TEAE	208/324	177/240	207/341	175/242
Safety population	**64.2%**	**73.8%**	**60.7%**	**72.3%**

Acknowledgements

- Fariba Izadi
- Rima Izem
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- Scott Komo
- And the fidaxomicin review team

Efficacy Assessment of Fidaxomicin

Rima Izem
FDA/CDER
Division of Biometrics 4

Anti-Infective Drugs Advisory Committee, April 5th 2011

From Assessments to Claims

EFFICACY ASSESSMENTS

Clinical Cure and Recurrence

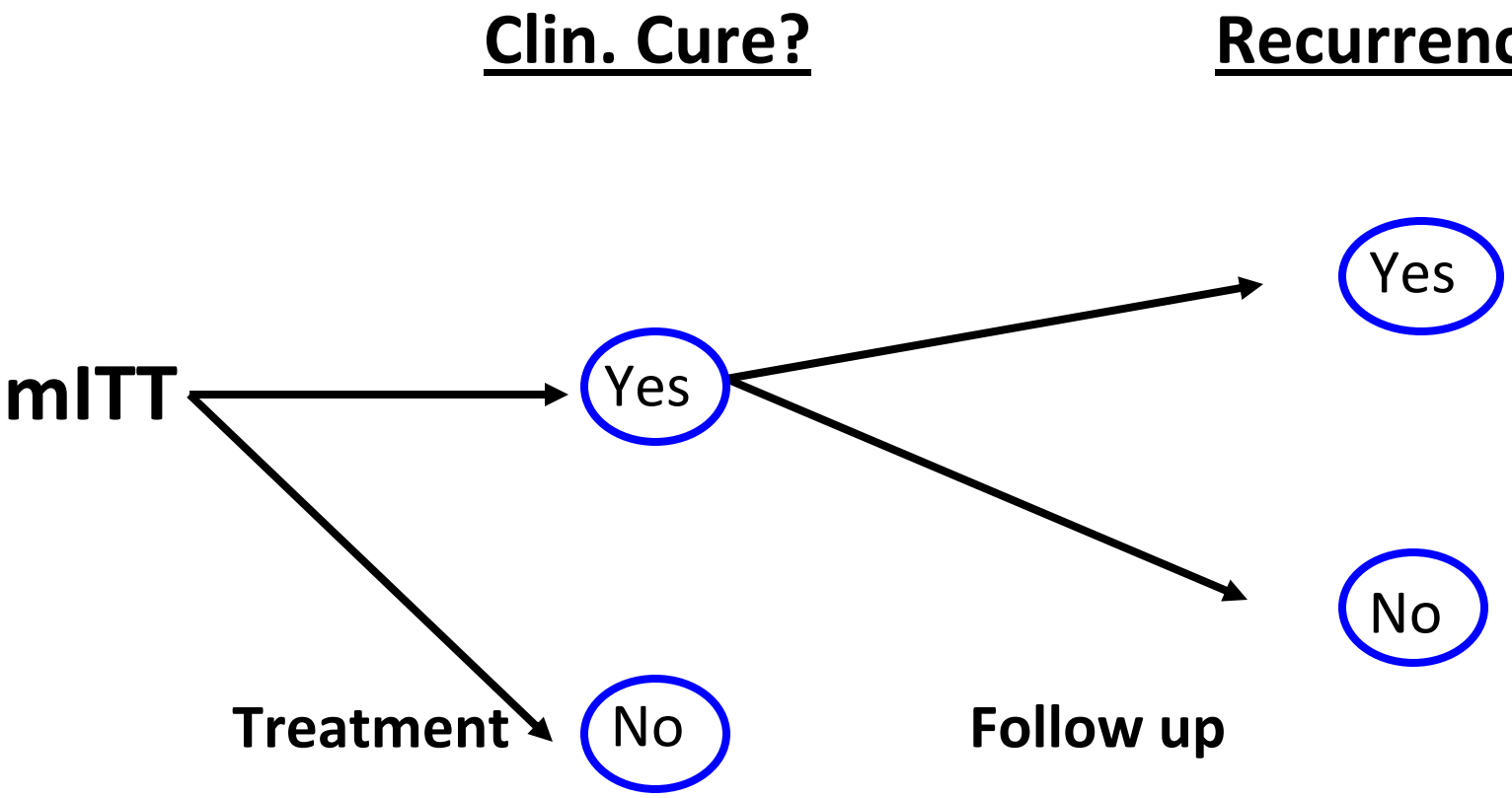
EFFICACY ENDPOINTS

Clinical Cure rate, Recurrence/Cure rate and Global Cure rate

INDICATIONS

Dificid™ (fidaxomicin tablets) for the **treatment of *Clostridium difficile* infection (CDI),** also known as *Clostridium difficile*-associated diarrhea (CDAD), and for **reducing the risk of recurrence when used for treatment of initial CDI**

Efficacy Assessments



Endpoints

Outcomes :

- Cure at EOT sustained at follow up
- Cure at EOT and recurrence at follow up
- Failure at EOT

Primary: Clin. Cure

YES

YES

NO

Secondary: Recurrence/Cure

NO

YES

Exploratory 003 & Secondary 004: Global Cure

YES

NO

NO

Main Points

- Efficacy at EOT and after follow up is best assessed by endpoints of **Clinical Cure Rate** and **Global Cure Rate** in mITT population

- Review supports
  - Non-inferiority of Fidaxomicin to Vancomycin for endpoint of Cure at day 10
  - Superiority of Fidaxomicin to Vancomycin for endpoint of Global Cure at study day 31 (or 21 days after end of treatment)

- In the Virulent strain of C. *Difficile* subgroup, there is no significant Global Cure difference between Fidaxomicin and Vancomycin

Recurrence/Cure and conditioning on different subsets

- Recurrence/Cure
  - In a given trt. arm: Risk of recurrence at follow up **when subj. cured in that trt arm at EOT**

- What does the **Δ (Recurrence/Cure)** mean?
  - Study 003:

  Age (Cured Fidaxomicin) < Age (Cured Vancomycin) (p=0.02)

  - Tolevamer: 3% vs Vancomycin: 23% (Louie et al, 2007)

  Baseline Severity (Cured in Tolevamer) < Baseline Severity (Cured in Vancomycin)

Alternative? Δ (Recurrence/mITT)

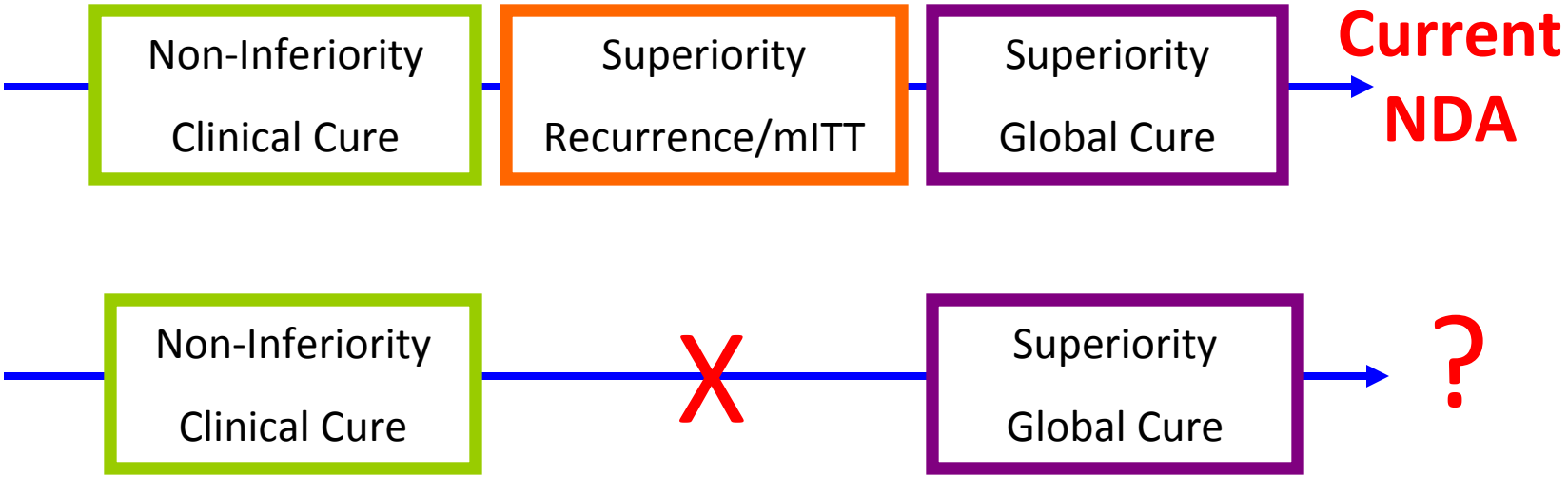
To results

What is "*reducing the risk of recurrence*" and how to quantify it?

- Which set of endpoints supports "reducing the risk of recurrence"? (Δ recurrence/mitt, Δ cure, Δ Global Cure)?

- What is the role of Gate-keeping testing strategy in this indication? Are other multiple testing strategies possible to support this indication?

"Reducing the risk of recurrence"?



Outline

- **Clinical Cure and sensitivity analysis**
  - **Non-inferiority margin**
  - **Clinical cure, applicant and FDA results**
- Global Cure, recurrence and sensitivity analyses
- Virulent strain subgroup results

Non-inferiority Margin for Clinical Cure

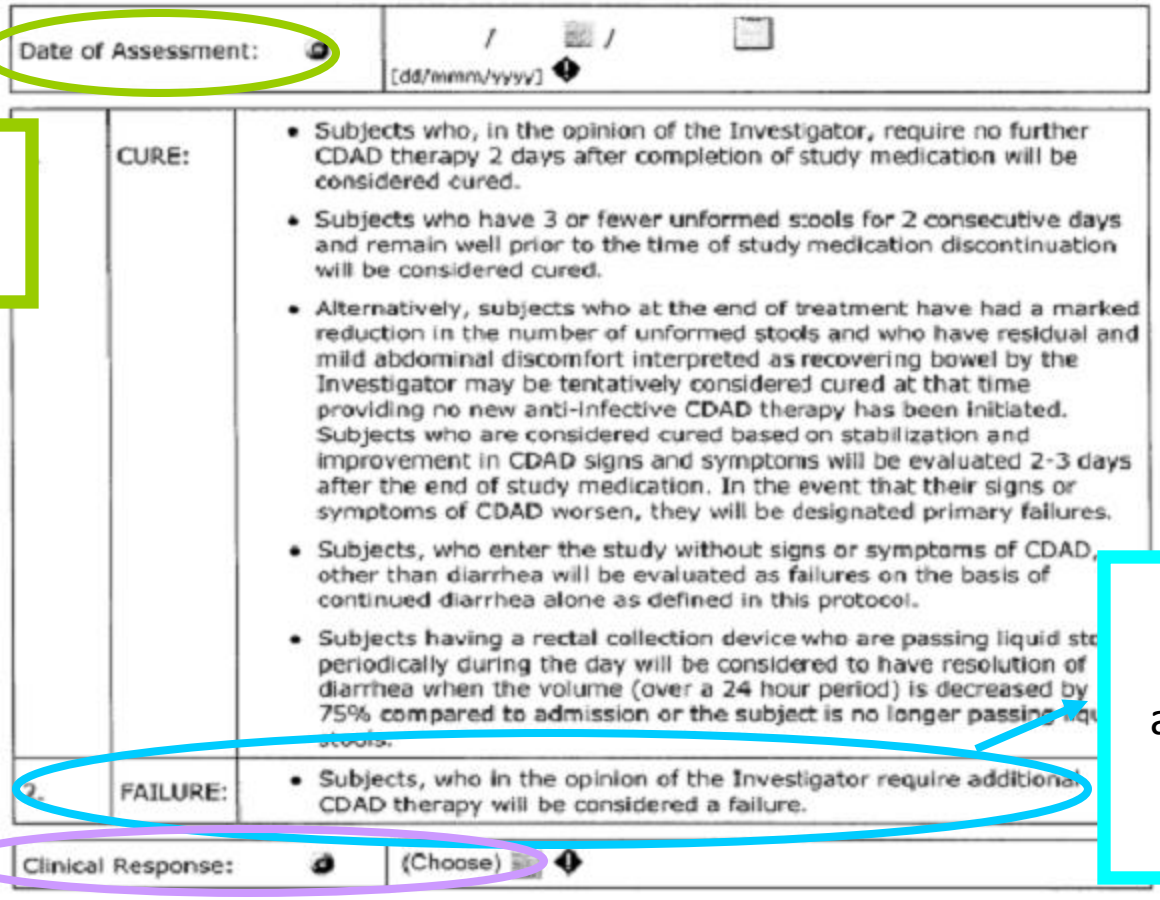
- NI margin for clinical cure is 10%

- NI margin derived from 2 large trials showing superiority of Vancomycin to Tolevamer (Louie et al 2006, Louie et al 2007, Bouza et al 2008 and Weiss 2009)

Clinical Cure Assessment

TOC: after EOT

TOC: days 10-12



Date of Assessment:		/ / [dd/mmm/yyyy]
	CURE:	• Subjects who, in the opinion of the Investigator, require no further CDAD therapy 2 days after completion of study medication will be considered cured. • Subjects who have 3 or fewer unformed stools for 2 consecutive days and remain well prior to the time of study medication discontinuation will be considered cured. • Alternatively, subjects who at the end of treatment have had a marked reduction in the number of unformed stools and who have residual and mild abdominal discomfort interpreted as recovering bowel by the Investigator may be tentatively considered cured at that time providing no new anti-infective CDAD therapy has been initiated. Subjects who are considered cured based on stabilization and improvement in CDAD signs and symptoms will be evaluated 2-3 days after the end of study medication. In the event that their signs or symptoms of CDAD worsen, they will be designated primary failures. • Subjects, who enter the study without signs or symptoms of CDAD, other than diarrhea will be evaluated as failures on the basis of continued diarrhea alone as defined in this protocol. • Subjects having a rectal collection device who are passing liquid st periodically during the day will be considered to have resolution of diarrhea when the volume (over a 24 hour period) is decreased by 75% compared to admission or the subject is no longer passing
2.	FAILURE:	• Subjects, who in the opinion of the Investigator require additional CDAD therapy will be considered a failure.
Clinical Response:		(Choose)

Failure: Require additional CDAD Therapy

ClinRO

Clinical Cure Results

Study	003		004	
Treatment (mITT)	Fidaxomicin (N= 289)	Vancomycin (N = 307)	Fidaxomicin (N = 253)	Vancomycin (N = 256)
Cure (applicant) n (%)	255 (88%)	263 (86%)	222 (88%)	222 (87%)
Inconsistencies	0	5	5	3
Cure (FDA) n (%)	255 (88%)	258 (84%)	217 (86%)	219 (85%)
Difference 95% CI	4.2% (-1.4%, 9.7%)		0.2% (-5.9%, 6.4%)	

Fidaxomicin is non-inferior to Vancomycin, i.e. LB of 95% CI > -10%

Conc. Med. list

Outline

- Cure and sensitivity analysis

- **Global Cure, recurrence and sensitivity analyses**
  - **Global Cure Definition and Time of Assessment**
  - **Inconsistencies with Global Cure**
  - **FDA Sensitivity Analyses**
  - **Results for recurrence/mITT**

- Virulent strain subgroup results

Recurrence Assessment

Rec. Assmt. Visit window:

Study days 36-40

ClinRo

1.	Date of Assessment:	/ / [dd/mmm/yyyy]
2.	RECURRENCE	• The re-establishment of diarrhea to an extent (frequency of passed unformed stools) that is than that noted on the last day of study medic with the demonstration of either toxin A or B f C. difficile and, in the Investigator's opinion we require retreatment with CDAD anti-infective t NOTE: Subjects being considered for recurrence mus positive toxin demonstrated in the stool. If a rapid s test is used and fails to demonstrate toxin, a confirm test using a non-rapid kit method must be used.
3.	NON-RECURRENCE	The maintenance of a non-diarrheal state up to and through the Poststudy Visit. Subjects who develop other causes of diarrhea associated with a negative *C. difficile* stool toxin test, will not be considered a recurrence.
4.	Recurrence	(Choose)
5.	Date of Recurrence	/ / [dd/mmm/yyyy] *(Hidden when CRF Protocol Version is before '2')*
6.	Time of Recurrence	: [24 hour clock] *(Hidden when CRF Protocol Version is before '2')*

+
D

Global Cure – Time of Assessment

Day 10 Day 17 Day 24 Day 31 Day 36-40

EOT **Follow up period after cure** **Rec. Assmt. Visit**

Clinical Cure + + **No Recurrence** → **Global Cure**

Clinical Cure + **no Diarrhea (Day 17-Day 31)** + **Missing** → **Global Cure**

Day 31: earliest protocol allowed day to assess Global Cure

Motivation for Sensitivity Analyses

Study	003		004	
Globally Cured (Applicant)	Fidaxomicin (N= 215)	Vancomycin (N = 197)	Fidaxomicin (N = 194)	Vancomycin (N = 162)
Total Inconsistencies with Global Cure	**18 (8%)**	**26 (13%)**	**18 (9%)**	**23 (14%)**
Death Before Study Day 31	4	6	8	4
CDAD Concomitant Med	12	18	12	13
Recurrence Assmt < day31	10	13	6	9

Conc. Med. List

Global Cure – Summary of Analyses

Applicant's results	Subgroups	Sensitivity 1	Sensitivity 2	Sensitivity 3
Yes	Deaths < day 31	No	No	Miss.
	Conc. Med + Diarrhea	No	No	No
	Conc. Med + Diarrhea?	No	Miss.	Miss.
	Rec. Assmt < day 31	No	Miss.	Miss.
	Other	Yes	Yes	Yes
No	Cure at EOT + Missing Recurrence	No	Miss.	Miss.
	Other	No	No	No

Sensitivity analyses pre-planned before total tally of inconsistencies

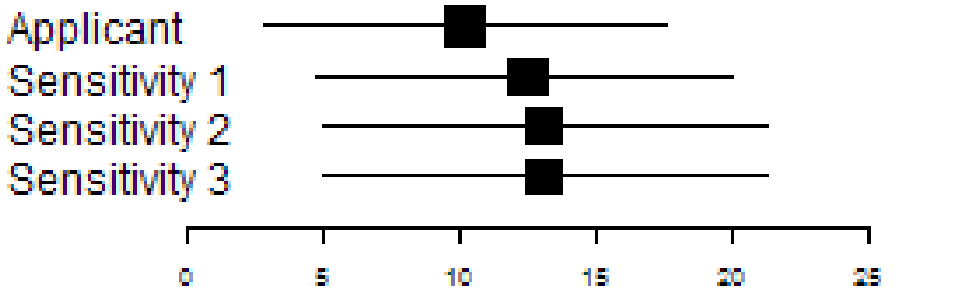
Sensitivity Analyses using Multiple Imputations

- Imputation step:
  - Chained Equation Algorithm (library mi in R) → 25 imputed datasets
  - Variables in imputation model: treatment, baseline characteristics, follow-up information for diarrhea and timing variables such as length of treatment
- CI for difference accounts for sampling variability and uncertainty due to missing values

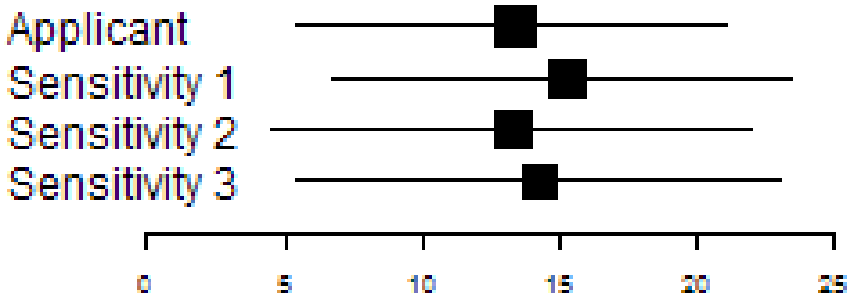
Global Cure Rate- Results

Study	Study 003		Study 004	
Treatment	Fidaxomicin (N= 289)	Vancomycin (N = 307)	Fidaxomicin (N = 253)	Vancomycin (N = 256)
Global Cure n (n/N)	215 (74%)	197 (64%)	194 (77%)	162 (63%)
Inconsistencies n (n/N)	18 (6%)	26 (8%)	18 (7%)	23 (9%)
Sensitivity 1	68%	56%	70%	54%
Sensitivity 2	71%	57%	72%	59%
Sensitivity 3	71%	58%	73%	59%

Global Cure Rate- Results



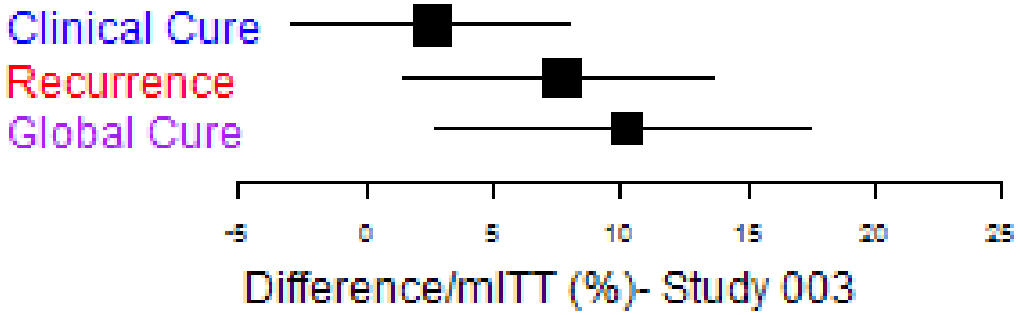
Difference in Global Cure Rate (%)- Study 003

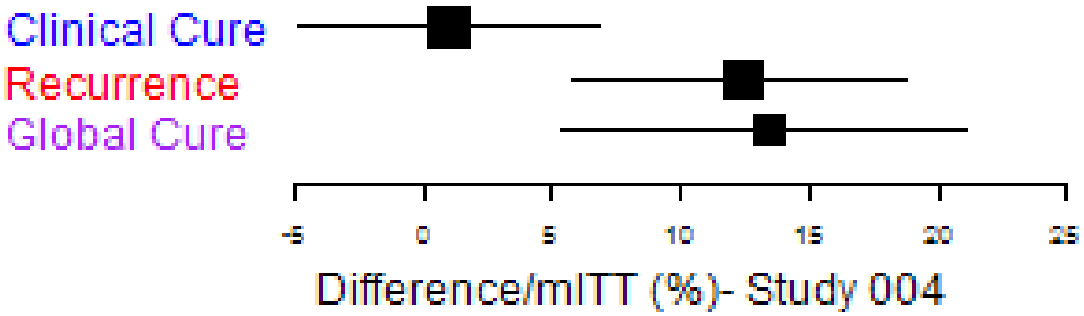


Difference in Global Cure Rate (%)- Study 004

Favors Vancomycin **Favors Fidaxomicin**

Clinical cure, Global Cure and Recurrence/mITT





Favors Vancomycin **Favors Fidaxomicin**

Back

Outline

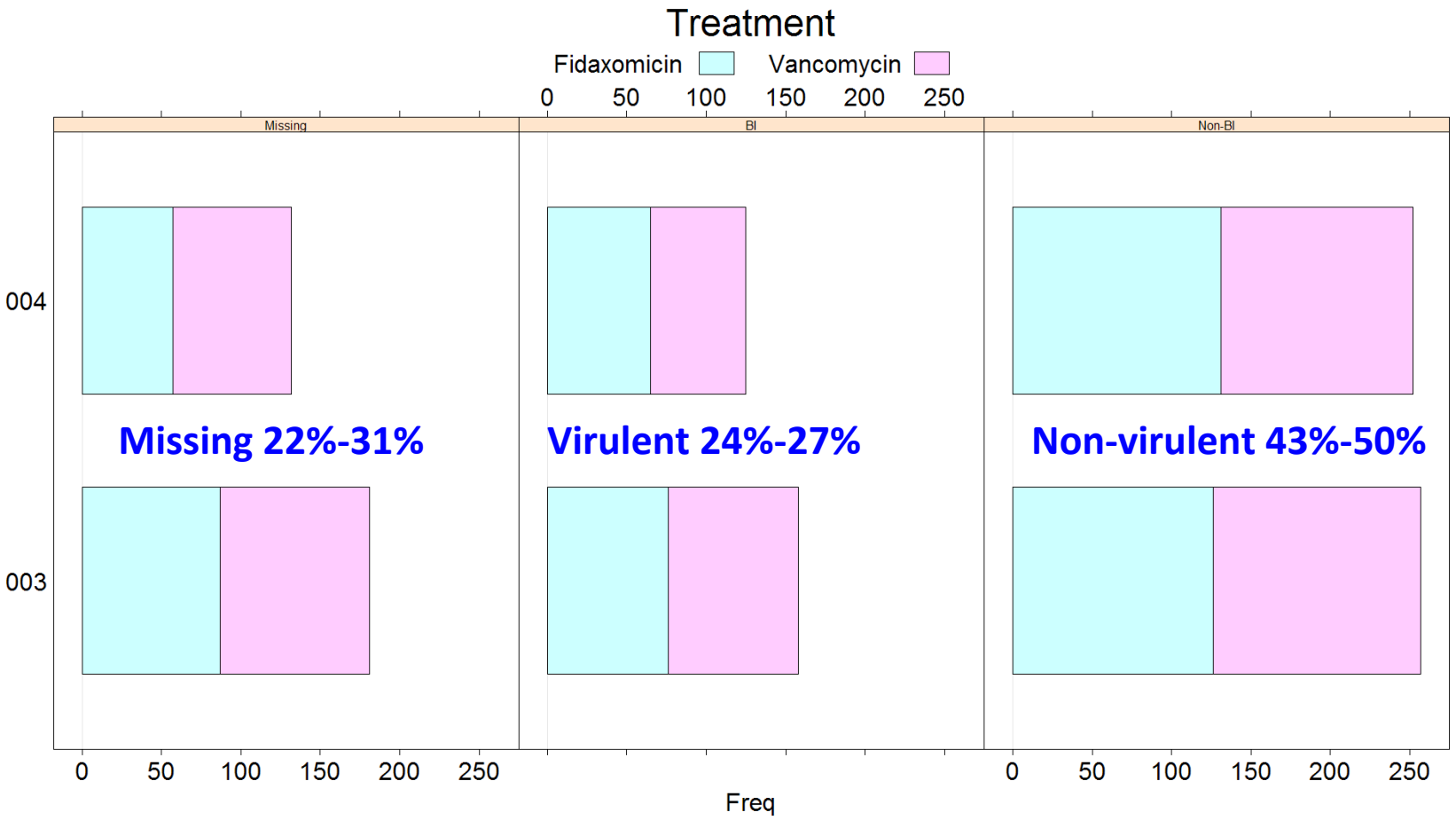
- Cure and sensitivity analysis
- Global Cure, recurrence and sensitivity analyses
- **Virulent strain subgroup results**

Subgroup Results

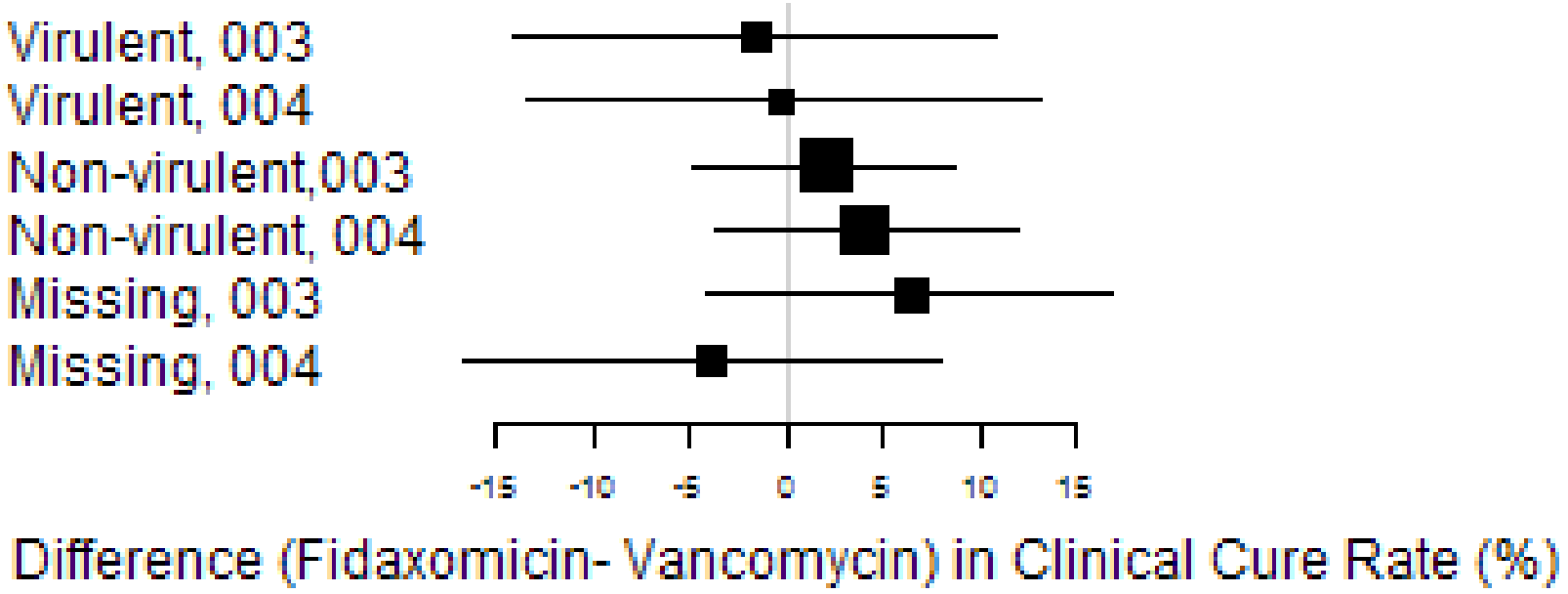
- Treatment effect (cure and global cure) is consistent in most subgroups (age, CDAD history…etc)

- Possible exception: virulent (BI) versus non-virulent (non-Bi).
  - Restriction Endonuclease Analysis (REA) group BI
  - "Epidemic" *C. difficile* strain (027/NAP1/BI) in US and Canada associated with more severe infection

Virulent/ Non-virulent strain

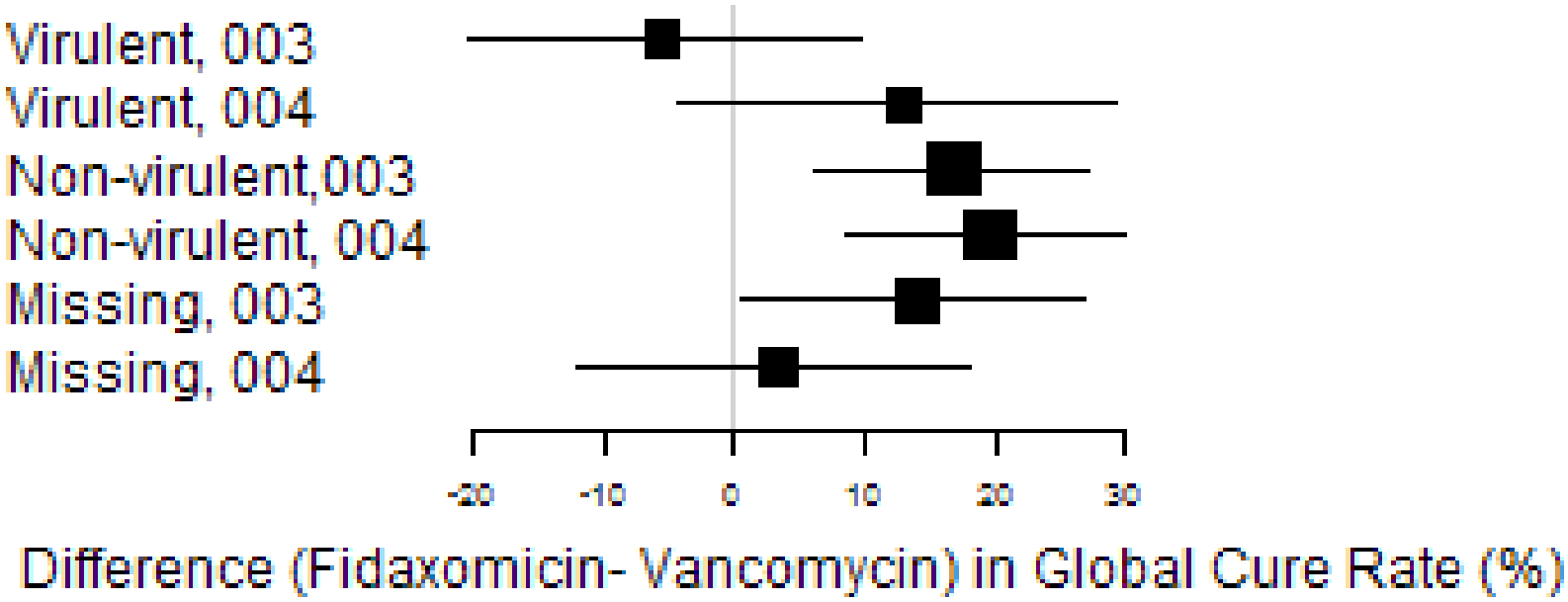


Virulent/Non-virulent Strain Clinical Cure



Favors Vancomycin ← **Favors Fidaxomicin** →

Virulent/ Non-virulent Strain Global Cure



Summary

- Efficacy at EOT and after follow up is best assessed by endpoints of **Clinical Cure Rate** and **Global Cure Rate** in mITT population

- Review supports
  - Non-inferiority of Fidaxomicin to Vancomycin for endpoint of Cure at day 10
  - Superiority of Fidaxomicin to Vancomycin for endpoint of Global Cure at study day 31 (or 21 days after end of treatment)

- In the Virulent strain of C. Difficile subgroup, there is no significant Global Cure difference between Fidaxomicin and Vancomycin

Back up slide

Concomitant Medication Treating CDAD

- Metronidazole
- Oral Vancomycin
- Rifaximin
- Nitazoxanide